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ORIGINAL ARTICLES

**ABNORMALITIES OF GROWTH.<sup>1</sup>**

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"THROUGHOUT the animate kingdom, from the simplest micro-organisms to the most complexly organized beings, that inexhaustible power of growth which ever since the genesis of the first protoplasm in the infinite past has created the structure of the fossil remains of former ages as well as our own existence—this capacity to grow, has remained as the most remarkable phenomenon of nature, the supreme riddle of life."<sup>2</sup>

The problems of growth have been studied in a diversity of ways, in accordance with the special training or talents of the students who have approached them as well as in response to the contemporary tendencies in the biological sciences. The very word, growth, has come to be applied with a variety of meanings. Thus we say that a crystal grows; that bacteria grow, when they multiply in number in a medium; that a tumor or a hydrocephalus grows when its mass becomes enlarged; that a child grows. Such heterogenous phenomena can scarcely be envisaged from a single viewpoint. For the present occasion, therefore, let us direct our interest primarily to man and the higher animals, in which growth may be regarded

<sup>1</sup> A paper presented before the Cleveland Academy of Medicine, May 12, 1916.

<sup>2</sup> Rubner, M., *Das Problem der Lebensdauer und seine Beziehung zum Wachstum*. München, 1908, p. 81; also *Ernährungsvorgänge beim Wachstum des Kindes*, Arch. f. Hyg., 1908, lxvi, 81.

for the most part as reduced to a minimum when the maximum average size has been reached.

Until quite recently most of the investigations of growth, in its normal as well as its pathological manifestations, have been morphological in character. This must not be interpreted as meaning that no other mode of study has been adopted. Statistics of changes in size and other features have been accumulated. Comparative analyses of growing structures have been attempted. The dynamics of the changes in growth likewise have become the subject for speculation in the past. But the dominance of the cell and its structural changes, and the popularity of cytology, embryology, cellular pathology and the newer "Entwicklungsmechanik," have overshadowed the conception of growth which realizes that increment in size means assimilation of food and the metabolism of matter. The comparative simplicity of structure of the "lower" organisms has encouraged the pursuit of the physiology of the unicellular forms in the hope that here the problems could be more easily unravelled. There is need, however, of going beyond the beginnings of the developmental processes and of supplementing the morphological methods of study. A knowledge of cell structure alone will not suffice to define growth. The size of the organism is also of much importance. "The science of nutrition," says Bayliss,<sup>3</sup> "would be almost impossible without the larger, warm-blooded animals. . . . The physiology of unicellular organisms, although of considerable importance in special aspects, is not to be regarded as 'general physiology.' Indeed, if the choice had to be made between the investigation of simple or complex organisms alone, there is no doubt that a much more general and fundamental body of doctrine would be obtained from the latter."

*The factors which determine the possibility of growth*, and upon which, therefore, any broad generalizations regarding the abnormalities of growth must be based may be classed, with respect to the organism involved, as internal or external in character. The *internal* factors include the real impulse to grow, of whatever nature it may be; in part they are inherited, they belong to the permanent biological characteristics of the individual. Heredity, with all that it involves, determines the most potent of these internal, constitutional incentives and conditions of growth. These are the determinants which are largely beyond our immediate control, yet must be reckoned with when defects of growth appear. The *external* factors that modify growth, on the other hand, are more amenable to directive regulation. The environment as well as the food of the individual can be modified more or less at will. Here, then, is a possible point of attack. If growth implies not only a capacity to grow, but also an actual increment of body substance, there must be

<sup>3</sup> Principles of General Physiology, 1915, p. 291.

an accession of nutriment from without. The character of the food, its utilization and metabolism in health and in disease are open to investigation. The study of nutrition in growth therefore probably offers the most promising of all the modes of approaching an understanding of this fundamental biological process.

In order to have a common basis for the discussion of the abnormalities of growth some definition is essential, difficult though it may be to formulate one in entirely satisfactory terms. Even when the body as a whole no longer gains in size, individual parts like the hairs and nails may continue to grow. It will be preferable to speak of such phenomena of localized growth as a renewal of tissues, and likewise to exclude from the category of real growth the deposition of fat and other reserve materials that often produce a gain in weight. "Increment in size" or "gain in weight" or "enlargement of mass" are inadequate descriptions of the more specific characteristics of the growth of the higher forms. I have found no more helpful concise definition than that by Schloss,<sup>4</sup> who characterizes growth as "*the correlated increase in the mass of the body, in definite intervals of time, and in a way characteristic of the species.*"

Perfect growth and development implies a far-reaching correlation of the various parts of the body. An upset in this nicely balanced relationship is speedily recognized as an anomaly. Energy and matter are insufficient to explain the consummation and maintenance of a normal as contrasted with an abnormal composition of the cells. The *specificity* of growth is something marked, particularly when normal is contrasted with perverted growth. The definition referred to above has a particular value in the analysis of abnormalities of growth because it immediately suggests some of the anomalies or irregularities. Abnormal growth may involve (1) the correlation feature, or (2) a time factor whereby the characteristic rate of the increase in mass is not maintained. The correlation refers, for example, to the arrangement of matter in respect to composition (proportions of protein, water, etc.) and likewise to form. When there is overgrowth of one part or underdevelopment of another the correlation is upset. This is an abnormality. Likewise when the change in size is well proportioned or correlated, but unduly delayed or prolonged, growth becomes abnormal in its rate for the individual under consideration.

There is no ideal index or measure of growth. The most common statistics and perhaps the most satisfactory individual data are those obtained for the increments of body weight. The diagrams show the so-called curves of growth for man and for the albino rat—an animal closely related in many features of growth which has formed the subject of extensive investigations in recent years.

With these general characteristics of changes in weight during the

<sup>4</sup> Die Pathologie des Wachstums im Säuglingsalter, Berlin, 1911, p. 4.

period of growth in mind we may consider Fig. 3, page 5, which indicates in a highly schematic form some of the abnormalities in the rate of growth seen in the development of the young.

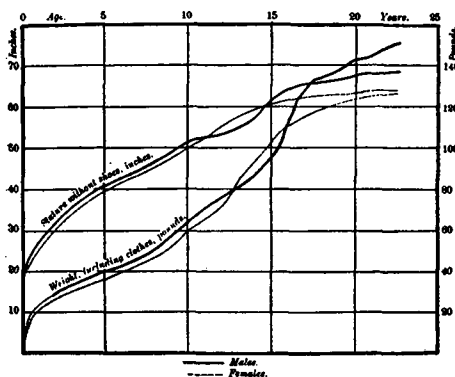


FIG. 1.—Diagram showing increase of stature and weight of both sexes, as determined by the Anthropometric Committee of the British Association. (From American Text-book of Physiology, 1896, p. 925.)

*Delayed growth* as the result of *external* factors can be brought about in a variety of ways associated with the food supply. Growth can be limited, of course, by an insufficient quantity of even the most appropriate food mixture. Again, there is a lower limit to

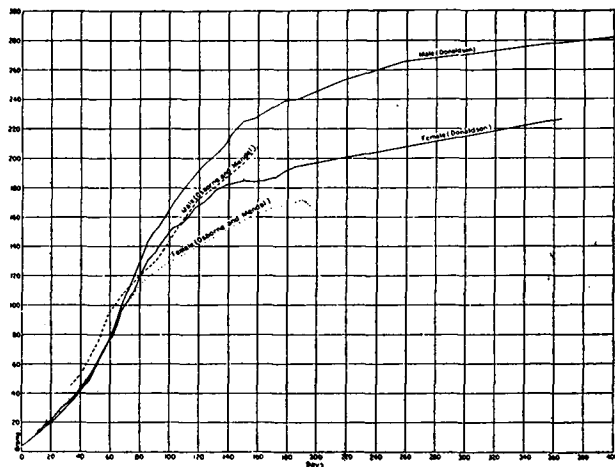


FIG. 2.—Curves of normal growth—rats. (From Osborne and Mendel and Donaldson.)

the quota of protein needed for normally rapid tissue construction, quite aside from an otherwise bountiful total energy supply. But even abundance of protein along with sufficient other nutrients may

not permit growth to continue normally, if the nitrogenous components of the diet fail to yield in suitable amounts every amino-acid required in tissue construction; for it is now an established belief among physiologists that certain of these nutrient units, such as cystine, lysine and tryptophane and doubtless others, are not constructed anew in the mammalian organism. They must be furnished as such, before new tissue containing them built up into its protoplasm can be elaborated. An appropriate supply of inorganic compounds, of lime and magnesium, of chlorid and phosphate, and perhaps of as yet unappreciated elements like iodine or manganese must sooner or later be available in the requisite minimum quantity. Finally, with all of these it now seems necessary to include a provision for the so-called food "accessories," the "vitamin<sup>5</sup>s" and

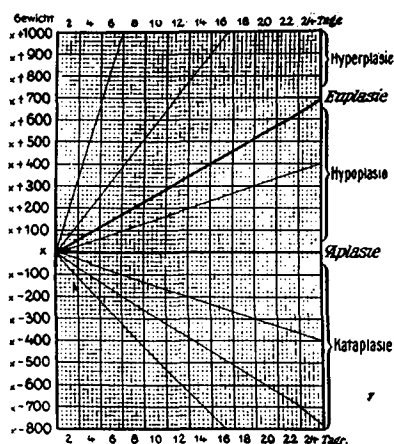


Fig. 3.—Schematic representation of abnormalities of growth. (From Schloss, *Die Pathologie des Wachstums im Säuglingsalter*, Berlin, 1911, p. 74.)

"auximones," which are believed to facilitate the nutrient processes and likewise, directly or indirectly, the process of growth. At any rate the failure to secure continued increment of body weight in young animals with an abundance of hitherto supposedly suitable but isolated and purified foodstuffs, and the prompt resumption of growth when very small addenda of certain natural products are furnished, leaves no other alternative than to give these accessories, seemingly insignificant though they may appear to be, due consideration in the problem of the food supply.

In discussing the nutrition of infancy Schlossmann<sup>5</sup> has remarked that the feeding of isodynamic quantities of food is not necessarily a guarantee of equal nutrient effects. The food must not only

<sup>5</sup> Beiträge zur Physiologie der Ernährung des Säuglings, Arch. f. Kinderheilkunde, liii, 1.

furnish equivalent amounts of energy, but also permit equivalent benefits to accrue to the individual that ingests it. Schlossmann therefore has suggested the term *isokerdic* ( $\tau\acute{o}$   $\kappa\acute{\epsilon}\rho\delta\omicron\varsigma$ , the gain) value to express for the equivalent biological utility of foods what the expression isodynamic indicates in respect to their comparable energy values. Repeatedly it has been observed that the addition of a seemingly insignificant amount of the non-protein, fat-free part of milk—such as the “protein-free milk” of Osborne and Mendel<sup>6</sup>—or of yeast (Hopkins,<sup>7</sup> Funk and Macallum<sup>8</sup>), or of plant parts containing the embryo<sup>9</sup> will suffice to convert failure on a given diet of isolated food substances into success. Even where one of this type of (presumably water-soluble) determinants is furnished growth may cease until some natural fat like butterfat, egg fat, or cod liver oil or

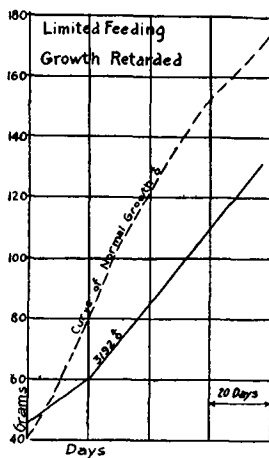


FIG. 4.—Curve of retarded growth due to limited feeding. (From Osborne and Mendel.)

fractions thereof are added to the diet. Essentials for growth that cannot be synthesized by the growing organism itself must be available in adequate amounts if the gains are to be normal in respect to the rate of growth—the time factor.

A few graphic illustrations of slow growth, exhibited in the form of curves of body weight and attributable to some of the various deficiencies of diet just discussed, are presented here. The first of these, Fig. 4, shows the effect of underfeeding with a qualitatively adequate food, in the case of albino rats.

<sup>6</sup> Carnegie Institution of Washington, Publication 156, Part II, 1911, p. 80.

<sup>7</sup> Feeding Experiments Illustrating the Importance of Accessory Factors in Normal Diets, *Jour. Physiol.*, 1912, xlv, 425.

<sup>8</sup> Studies on Growth. II. On the Probable Nature of the Substance Promoting Growth in Young Animals, *Jour. Biol. Chem.*, 1915, xxiii, 413–421.

<sup>9</sup> McCollum, E. V., and Davis, M., The Essential Factors in the Diet During Growth, *Jour. Biol. Chem.*, 1915, xxiii, 231–246.

Fig. 5 shows the results of diets low and high respectively in the same protein.

In Fig. 6 the deficiency is exemplified by a low content of inorganic salts.

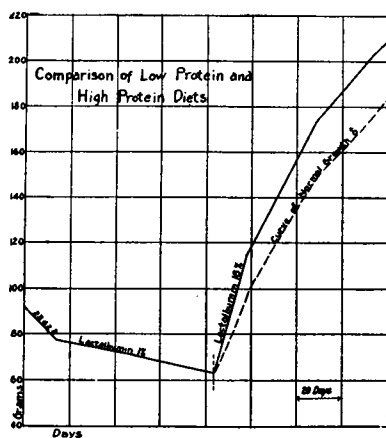


FIG. 5.—Curve showing comparative effects of diets, high and low respectively, in the same protein. (From Osborne and Mendel.)

The retarded growth, with final cessation of increase in size, seen in Fig. 7, is attributable to the lack of suitable “food accessories” in the diet.

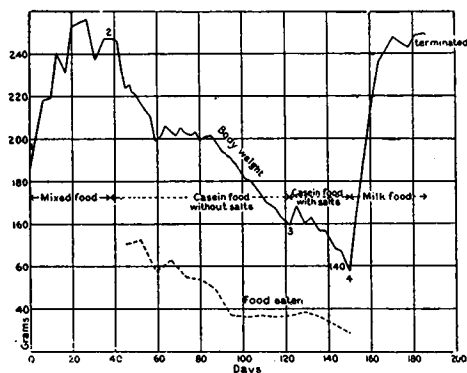


FIG. 6.—Showing effect of deficiency of inorganic salts in the diet upon growth. (From Osborne and Mendel.)

In Fig. 8 responsibility for the slow growth observed rests upon the character of the proteins fed, which failed to yield all of the amino-acids in suitable abundance.

In the preceding illustrations the growth manifested by the animals has usually been uninterrupted though proceeding at a decidedly slower rate than is normal for the species. Similar experi-

ences are familiar in the clinic for infants, but it is usually impossible to relate the retardation to a known factor as has been done in the experimental cases cited. Let there be no misunderstanding in the sense that we are attempting to refer all retardations of growth to external or dietary factors. It is merely this type of abnormality in the time relations or rate of growth that concerns us here for the moment.

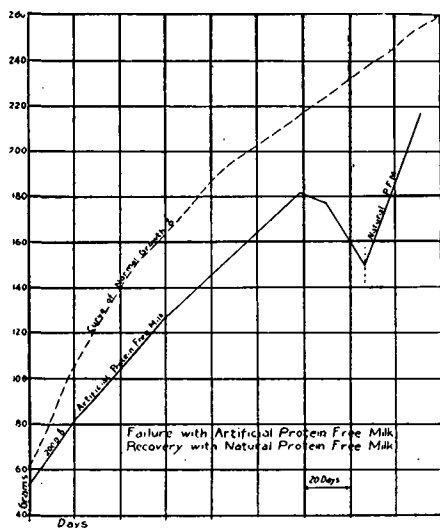


FIG. 7.—Showing effect of lack of suitable "food accessories" in the diet upon growth. (From Osborne and Mendel.)

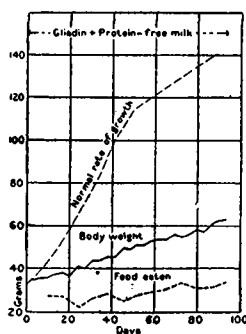


FIG. 8.—Showing failure to grow on a diet containing gliadin as the protein component. (From Osborne and Mendel.)

*Complete cessation of growth* in individuals not fully grown up may represent a more aggravated deprivation of some food factor essential for tissue construction—a status in which there is neither gain nor loss of weight. Such failure to grow may be observed

not only where the food supply is scanty but even where the energy content of the diet is evidently liberal. Some of the instances of "stunting" which Osborne and I have observed in our experiments with rats have been surprising in respect to the duration of the period of failure to grow. Illustrations of different types of "stunting" are shown in the following charts:

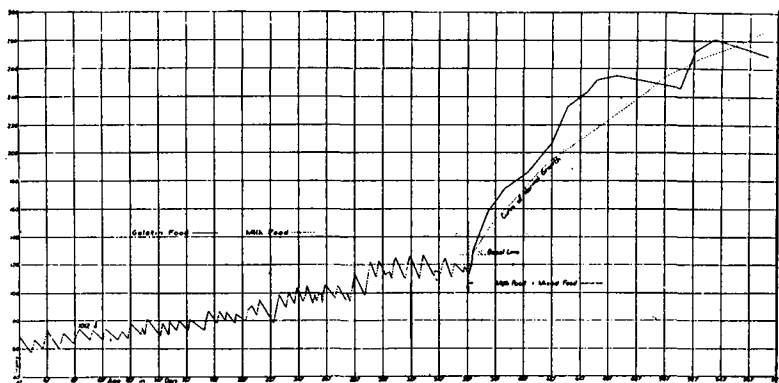


FIG. 9.—Showing prolonged failure to grow owing to inadequate character of the ration. (From Osborne and Mendel.)

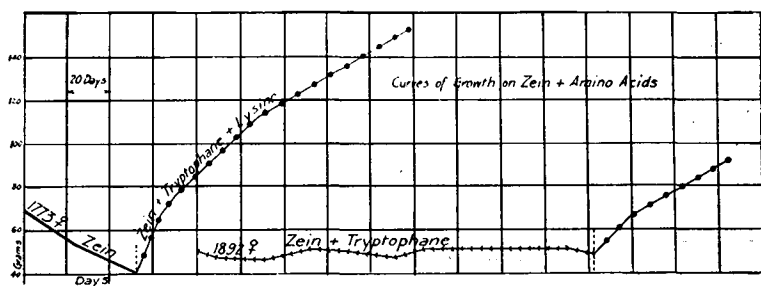


FIG. 10.—Showing failure to grow owing to a lack of the amino-acid lysine in the diet. (From Osborne and Mendel.)

Examples of this type of abnormality of growth could also readily be collected from human experience, although an equally long duration of the suppression of growth in terms of the total span of life has probably never been recorded for man. In the charts just presented it will be noted that growth was resumed in every case when an *external* factor, the diet, was altered. We are dealing here with retention of infantile characters and the capacity to grow, in many of the cases cited, at a period long beyond that at which growth is usually completed. The resumption and completion of growth after long-continued failure to grow may seem surprising in view of the wide-spread impressions that the growth impulse declines with

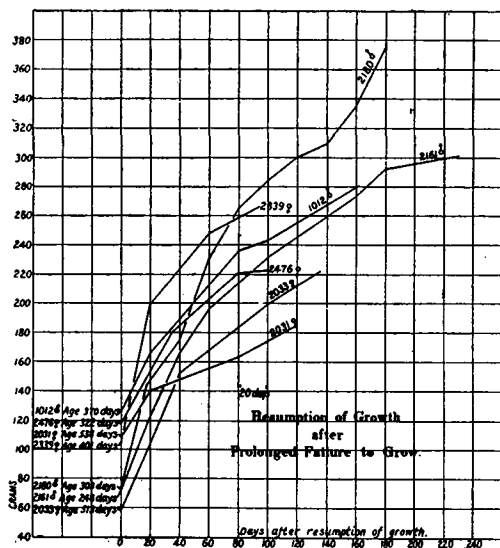
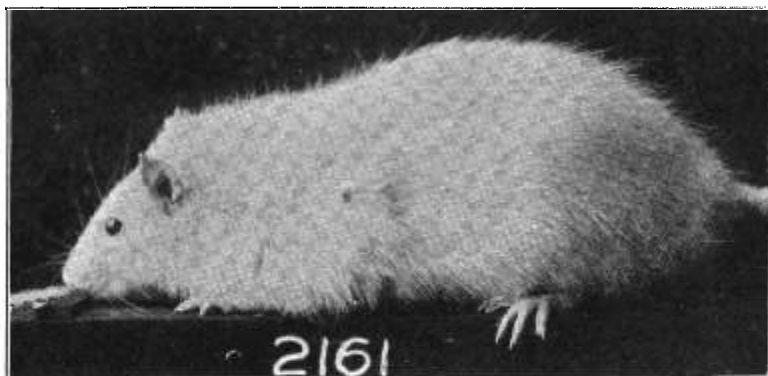


FIG. 11.—Showing resumption of growth in rats after prolonged period of suppression of growth. (From Osborne and Mendel.)



age. A few records are graphically represented in Figs. 11 and 12. The record of an infant showing a very brief delay in growth is given in Fig. 13.

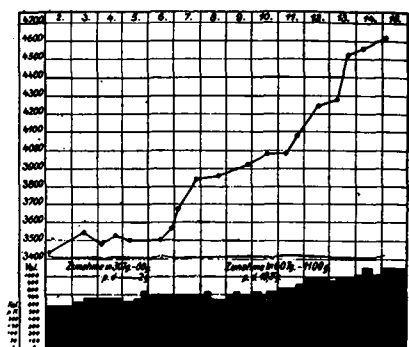


FIG. 13.—Showing the curve of suppression and resumption of growth in an infant. (From Langstein und Meyer, *Säuglingsernährung und Säuglingsstoffwechsel*, 1910, p. 68.)

The results of our investigation in this field have been summarized as follows:

"The growth impulse, or capacity to grow, can be retained and exercised at periods far beyond the age at which growth ordinarily ceases. In the case of our experimental animals, albino rats, in which increment of body weight ordinarily ceases before the age of 300 days, resumption and completion of growth were readily obtained at an age of more than 550 days. It is now reasonable to ask whether the capacity to grow can ever be lost unless it is exercised.

"Even after *very prolonged* periods of suppression of growth, the rats can subsequently reach the *full size* characteristic of their species. In this respect there is no impairment of the individual.

"The satisfactory resumption of growth can be attained not only after stunting by underfeeding, but also after the cessation of growth which results when the diet contains proteins unsuitable for the synthetic processes of growth or is low in protein.

"Growth in the cases referred to is resumed at a rate normal for the size of the animal at the time. It need not be slow, and frequently it actually exceeds the usual progress.

"The size or age at which the inhibition of growth is effected does not alter the capacity to resume growth. Even when the suppression of growth is attempted for very long periods at a very small size (body weight) the restoration may be adequate when a suitable diet is furnished.

"The procreative functions are not necessarily lost by prolonged failure to grow before the stage of development at which breeding ordinarily possible.

"The period of growth may be greatly prolonged by inadequacies in the diet, so that growth becomes very slow without being com-

pletely inhibited. Though the time of reaching full size is thus greatly delayed, growth, as expressed by suitable body weight, can ultimately be completed even during the course of long-continued retardation.

"The methods of partially retarding or completely suppressing growth are too varied and unlike to permit final answers as yet regarding the outcome of all of the procedures of inhibition for the subsequent welfare of the individual. Our observations apply to the effects upon size and a few other incidental features mentioned. Although it is doubtful whether the fundamental features will be altered, far reaching dogmatic statements are scarcely justifiable until the experiments have been extended to include other factors and animal species."<sup>10</sup>

Loss of weight, or *negative growth*, as it has been termed, is familiar not only as a manifestation of specific disease, but also as the result of malnutrition of dietary origin. Here, too, altered food supply may bring restoration of normal conditions. The "curve of repair" is unique in the rate at which changes in weight usually take place. The restoration which may follow a loss of tissues, etc., even in adult life, exceeds in its rapidity even that observed at the most vigorous periods of growth. Clinicians are well aware that recovery of weight lost during illness may take place with surprising rapidity. It seems as if the depleted body cells were ready in structure for the return of missing components without the necessity of a reconstruction of the entire fabric of the wasted tissues. A graphic expression of this is seen in Fig. 14.

Anomalies of growth expressed by an *exaggerated rate of growth* are among the rarities. Whenever the growth of an entire organism as well as that of individual organs is modified in the sense of acceleration, this usually involves repair—the reversal or return of a morbid condition to the normal as it has just been illustrated. Attention has lately been directed to the unexpectedly accelerated rate at which the increment of body weight may be resumed after growth has, for some reason or other, been inhibited for a time.<sup>11</sup> Fig. 15 shows that "after periods of suppression of growth, even without loss of body weight, growth may proceed at an exaggerated rate for a considerable period. This is regarded as something apart from the rapid gains of weight in the repair or recuperation of tissue actually lost. Despite failure to grow for some time the average normal size may thus be regained before the usual period of growth is ended."

Analogous conditions in infants seem to be represented by the

<sup>10</sup> Osborne and Mendel, The Resumption of Growth after Long-continued Failure to Grow, Jour. Biol. Chem., 1915, xxiii, 439-454.

<sup>11</sup> Osborne and Mendel, Acceleration of Growth after Retardation, Am. Jour. Physiol., 1916, xl, 16-20.

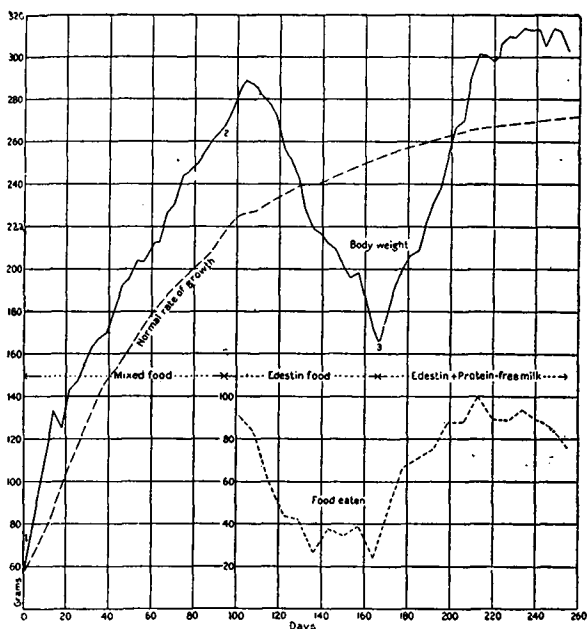


FIG. 14.—Curves showing restoration after depletion of body weight in rats.  
(From Osborne and Mendel.)

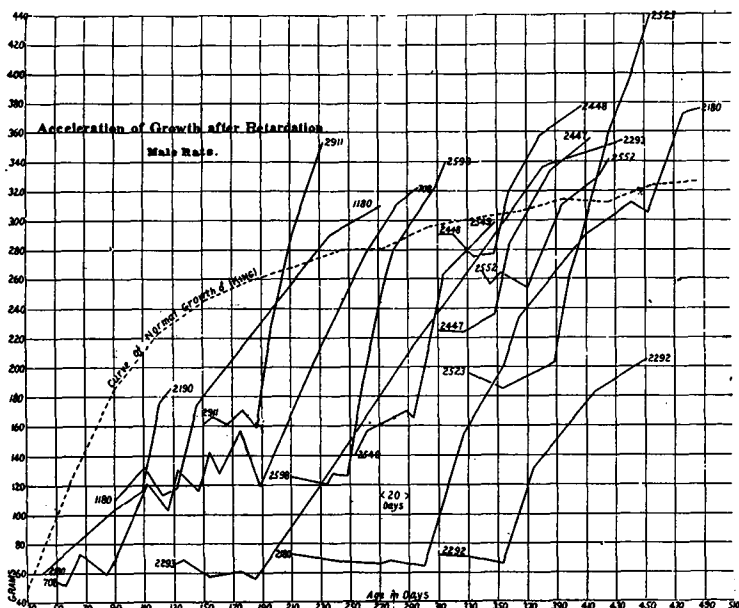


FIG. 15.—Showing curves of acceleration of growth after retardation of growth.  
(From Osborne and Mendel.)

following case of failure to gain weight in scurvy and the resumption of growth under the influence of orange juice added to the diet.<sup>12</sup>

The foregoing experiences respecting the ability of the individual to make exceptionally rapid gains of weight after periods of enforced maintenance without growth have led us to raise certain questions of broader biological interest. "What has time accomplished in the interval of unchanged total body weight? Have developmental changes or cellular rearrangements proceeded? Have some of the cells (perhaps those of certain endocrine glands) advanced in their development more nearly normally than the great mass of the tissues? If so, they might exert an undue stimulus upon the energy transformations leading to growth."<sup>13</sup> The inquiries here submitted may properly introduce a second phase of our subject, the *abnormalities*

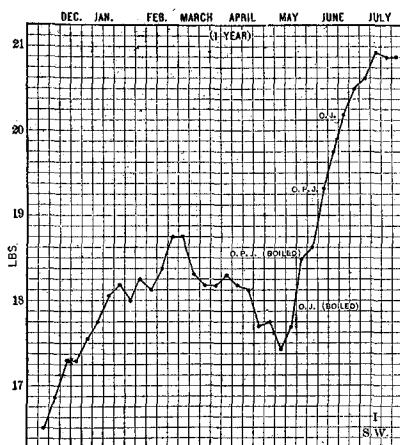


FIG. 16.—Showing curve of accelerated growth in an infant after failure to grow. (From Hess, 1916.)

of correlation in growth. The interrelations of proportion in the parts of the body may vary not only among individuals and species, but also in the same individual at different stages of development, as is shown in Fig. 17.

Precisely as there are changes in the correlation of form or morphological structure, so there may be alterations in the distribution of chemical components of the body, the upset of which represents abnormality. Thus Aron has indicated that the form of animals maintained at stationary weight before they are fully grown may change. They may grow in stature, one part changing at the

<sup>12</sup> Hess, A. F., The Influence of Infantile Scurvy on Growth (Length and Weight), *Proc. Soc. Exper. Biol. and Med.*, 1915, xiii, 50.

<sup>13</sup> Osborne and Mendel, Acceleration of Growth after Retardation, *Am. Jour. Physiol.*, 1916, xl, 16.

expense of another.<sup>14</sup> This is seen in Fig. 18, in which the same rat was photographed at intervals of forty-seven days, during which there was no increment in total weight.

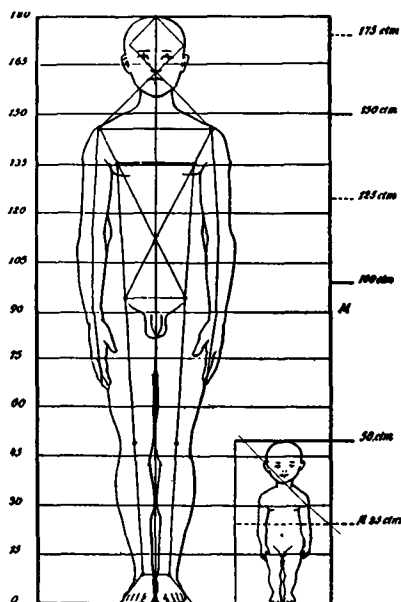


FIG. 17.—Showing changed proportions of the body of man accompanying growth. (From Stratz, *Der Körper des Kindes*, 1904, p. 57.)

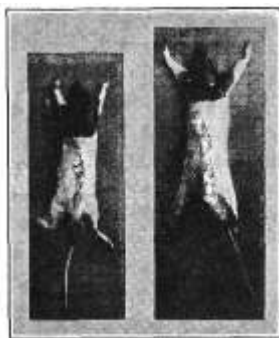


FIG. 18.—Showing changes of form with stationary body weight. (From Aron, 1912.)

The change of form noted by Waters<sup>15</sup> in young cattle underfed so as to keep their weight stationary is also evidence of correlative

<sup>14</sup> Aron, H., Weitere Untersuchungen über die Beeinflussung des Wachstums durch die Ernährung. Verhandlungen der 29sten Versammlung der Gesellschaft für Kinderheilkunde in der Abteilung für Kinderheilkunde der 84. Versammlung der Gesellschaft deutscher Naturforscher und Aerzte in Münster, 1912, 99-103.

<sup>15</sup> The Influence of Nutrition upon the Animal Form, Proceedings of the Society for the Promotion of Agricultural Science, 1909, xxx, 70; also XVII. Biennial Report, Kansas State Board of Agriculture, 1911, xxii, 199.

changes. Apparently the skeleton has grown in these cases at the expense of other parts. It is doubtless true, as Aron has indicated, and as has been shown in unpublished experiments by Dr. Judson in the writer's laboratory, that the inorganic components of the skeletal parts may continue to increase while the body, as a whole, is failing to gain in weight.

Defective bone growth is undoubtedly concerned in a variety of abnormalities of development. A quotation from McCrudden<sup>16</sup> may serve to illustrate some of the problems involved:

"Another kind of condition in which bone growth is involved is dwarfism. The causes are probably many. But in one type I have observed a disturbance of calcium metabolism associated with improper development of bone. Calcium is almost absent from the urine, leading to the belief that the blood must be poor in calcium or contain it in some unusual combination. The feces are very rich in calcium, containing sometimes more than the food. There is, in fact, a flux of calcium through the feces. And in these cases the long bones fracture easily and roentgen-ray examination shows a very thin cortex. In other types there are no abnormalities of this kind. Now, as pointed out by Rubner, we can imagine two fundamental causes for the lack of growth: (1) the lack of what might be called the tendency to grow, that property which is present in young animals, but absent in adults, and (2) the absence of the material for growth. And it seems to me that in these two types we have examples of disturbances of each of these two factors. In the one the skeleton is growing as fast as the material at its command permits. We might almost say that it is growing too fast, for it is growing in length at the expense of solidity. In the other there is no such tendency to grow. There is calcium enough present to form longer bones, but there is no tendency to form them. And this kind of disturbance of bone nutrition we may refer to as a quantitative change, for the bones fail to grow in size. There are two large subdivisions of this type—one in which the tendency to grow is absent, the other in which the material for growth is not available."

There is occasion to believe that the growth of bone in the young is only one of the developmental processes under the physiological dominance, so to speak, of the endocrine or ductless glands. The thyroid, thymus, ovary, testis, hypophysis and others, furnishing inhibitory as well as facilitating factors, may be involved. The effects of removal or loss of function of some of these glands upon growth are being investigated in a more systematic manner. The results of gonadectomy are perhaps most familiar. Many of the peculiar phenomena in respect to the evolution of stature, the secondary sex characters, psychical aberrations and their deviations from the usual mode of development induced by experiments in

<sup>16</sup> The Nutrition and Growth of Bone, Transactions of XV International Congress on Hygiene and Demography, Washington, September 23-28, 1912.

growth find an analogue in human cases of infantilism.<sup>17</sup> Sexual infantilism must be differentiated from another abnormality of childhood to which Herter<sup>18</sup> gave the name *intestinal infantilism*. This is a pathological state marked by a striking retardation in growth of the skeleton, the muscles and the various organs and associated with a chronic intestinal infection characterized by the overgrowth and persistence of bacterial flora belonging normally to the nursling period. The chief manifestations of intestinal infantilism are: Arrest in the development of the body; maintenance of good mental powers and a fair development of the brain; marked abdominal distention; a slight or moderate or considerable degree of simple anemia; the rapid onset of physical and mental fatigue; irregularities of intestinal digestion resulting in frequent diarrheal seizures. A type of infantilism associated with poor nutrition due to the defective circulation dependent on a congenital or acquired cardiac defect (*vitium cordis*) is shown in Fig. 19.



FIG. 19.—Showing infantilism in a youth, aged sixteen years, in contrast with a normal individual of the same age. (From Peritz, 1911, p. 460.)

It will be noted that the interferences with normal growth may be constitutional, or internal, in some of these manifestations of abnormalities of correlation, and external or seemingly associated with alimentation in other cases. It is not yet possible to distinguish clearly between cause and effect. Normal development of the endocrine glands (upon which in turn properly correlated growth depends) may often be conditioned upon a suitable food supply. It is thus quite conceivable, as several writers have pointed out, that the inevitable need of specific amino-acids or "food accessories" is

<sup>17</sup> Peritz, G., *Der Infantilismus*. Ergebnisse der inneren Medizin und Kinderheilkunde, 1911, xvii, 405.

<sup>18</sup> On Infantilism from Chronic Intestinal Infection, New York, 1908.

occasioned not alone by its value as a direct constructive unit in the growing body, but equally well because it plays some role in facilitating the function of some ductless gland. The supposed relation of iodine to the thyroid gland at once presents itself as a possible illustration. Complex pluriglandular regulatory inter-relations have often been discussed of late.

Only hasty and fragmentary reference can be made here to the more recent interesting observations of Cushing,<sup>19</sup> Goetsch,<sup>20</sup> and others on the possible relations of the pituitary gland and its disorders to growth; to the investigations of McCord<sup>21</sup> and of Dandy<sup>22</sup> on the pineal body; to the studies of Pearl,<sup>23</sup> Robertson,<sup>24</sup> and others on the feeding of pituitary and corpus luteum to growing animals.

It is too early to draw any sweeping conclusions from the already extensive literature on the ductless glands; but one may look forward with confidence to interesting developments in this field of the physiology and pathology of growth. Future investigation may show that directive influences in growth reside in the endocrine glands to an extent scarcely realized at present; possibly it will be found that the correlative factor which has been emphasized in this review is closely bound up even more closely than can now be appreciated with the proper growth and development of such special tissues.

A remarkable illustration of the potent effect of substances derived from the ductless glands has been furnished by Guder-natsch<sup>25</sup> and verified and extended by other investigators (Romeis<sup>26</sup>

<sup>19</sup> *The Pituitary Body and its Disorders*, Philadelphia, 1912.

<sup>20</sup> *The Influence of Pituitary Feeding upon Growth and Sexual Development*, Bull. Johns Hopkins Hosp., 1916, xxvii, 29.

<sup>21</sup> *The Pineal Gland in Relation to Somatic, Sexual and Mental Development*, Jour. Am. Med. Assn., 1914, lxiii, 232-235. *The Pineal Gland in Relation to Somatic, Sexual and Mental Development*, second paper, Jour. Am. Med. Assn., 1915, lxx, 517-520.

<sup>22</sup> Jour. Exper. Med., 1915, xxii, 237.

<sup>23</sup> *Studies on the Physiology of Reproduction in the Domestic Fowl*. XIV. *The Effect of Feeding Pituitary Substance and Corpus Luteum Substance on Egg Production and Growth*, Jour. Biol. Chem., 1916, xxiv, 123-135.

<sup>24</sup> *Experimental Studies on Growth*. III. *The Influence of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse*, Jour. Biol. Chem., 1916, xxiv, 385-396. *Experimental Studies on Growth*. IV. *The Influence of Tethelin, the Growth-controlling Principle of the Anterior Lobe of the Pituitary Body upon the Growth of the White Mouse*, Jour. Biol. Chem., 1916, xxiv, 397-408.

<sup>25</sup> *Feeding Experiments on Tadpoles*. I. *The Influence of Specific Organs Given as Food on Growth and Differentiation*, Archiv f. Entwicklungsmechanik der Organismen, 1912, xxxv, 457-483. *Feeding Experiments on Tadpoles*. II. *A Further Contribution to the Knowledge of Organs with Internal Secretion*, Am. Jour. Anat., 1914, xv, 431-474. *Feeding Experiments on Rats*. III. *A Further Contribution to the Knowledge of the Organs with an Internal Secretion*, Am. Jour. Physiol., 1915, xxxvi, 370-379.

<sup>26</sup> *Der Einfluss verschiedenartiger Ernährung auf die Regeneration bei Kaulquappen (Rana esculenta)*. I. Archiv f. Entwicklungsmechanik der Organismen, 1913, xxxviii, 183. *Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe*. II. *Einfluss von Thyroidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven*, Archiv f. Entwicklungsmechanik der Organismen, 1914, xl, 571.

and Cotronei<sup>27</sup>). A number of mammalian organs, especially those with an internal secretion: thyroid, thymus, adrenal, testis, ovary, hypophysis, liver, muscle, etc., were given as food to tadpoles of *Rana temporaria* and *esculenta*. It was seen that each organ exerted a certain influence on growth and differentiation of the animals. Most striking was the influence of the thyroid food. It caused a precocious differentiation of the body, but suppressed further growth. The tadpoles began to metamorphose a few days after the first application of the thyroid, and weeks before the control animals did so. The influence of the thymus was quite the opposite. Especially during the first days of its application it caused a rapid growth of the animals, but postponed the final metamorphosis or suppressed it completely. The appearance of tadpoles fed on thymus and thyroid respectively is shown in Fig. 20.

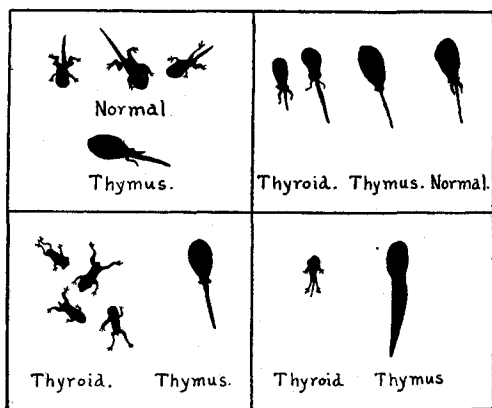


FIG. 20.—Showing effects of feeding thyroid and thymus to tadpoles.

Abderhalden,<sup>28</sup> from whose paper part of these illustrations are taken, has found that the thymus, thyroid, and other glands may be subjected to digestion by pepsin, trypsin, and erepsin successively, until the protein test is no longer obtainable; yet the products of digestion still contain the substances which either promote or suppress differentiation and modify growth. Combinations of several glands fed simultaneously may produce grotesque animal forms. A new field of investigation has been opened.

In the future it will be necessary to reckon with the probability

<sup>27</sup> Première contribution expérimentale à l'étude des rapports des organes dans la croissance et dans la métamorphose des Amphibies anoures. L'influence de la nutrition avec la thyroïde des mammifères, Archives italiennes de biologie, 1915, lxi, 305.

<sup>28</sup> Studien über die von einzelnen Organen hervorgebrachten Substanzen mit spezifischer Wirkung. I. Verbindungen, die einen Einfluss auf die Entwicklung und den Zustand bestimmter Gewebe ausüben, Pflüger's Arch., 1915, clxii, 99.

that growth in the sense in which we have defined it is dependent upon many factors, some of which facilitate, while others may retard the orderly progress of the process. A given environment may be disadvantageous, not only because it presents harmful or inhibitory influences, but also because it fails to manifest those that promote growth. The effect which nutrition may exert is only part of the story of growth; but it is a factor regarding which helpful information is being accumulated and one which is subject to immediate modification in a way that hereditary factors are not. Much commendable effort is being expended in improving the environment of the human individual during the period of growth. The current interest in the food hygiene of infancy, the school lunch problem, and related topics bear witness to this. These endeavors in the field of enlightened philanthropy, and public welfare should rest, as far as present-day knowledge will permit, on the basis of scientific information.

Traditions regarding growth and its perversions must give way to tested truths. It matters little if some of the determinants have not yet been discovered—if the limited experience of the laboratory fails to cover all the problems of the home and the clinic. Some real progress has been revealed, so that there is a sense of satisfaction even in relation to the obscure questions which have here been reviewed, in hearing Karl Pearson's<sup>29</sup> conclusion respecting the claims of science. He says: "For the present, then, it is better to be content with the fraction of a right solution than to beguile ourselves with the whole of a wrong solution. The former is at least a step toward the truth, and shows us the direction in which other steps may be taken. The latter cannot be in entire accordance with our past or future experience, and will therefore ultimately fail to satisfy the æsthetic judgment. Step by step that judgment, restless under the growth of positive knowledge, has discarded creed after creed, and philosophic system after philosophic system. Surely we might now be content to learn from the pages of history that only little by little, slowly line upon line, man, by the aid of organized observation and careful reasoning, can hope to reach knowledge of the truth, that science, in the broadest sense of the word, is the sole gateway to a knowledge which can harmonize with our past as well as with our possible future experience. As Clifford puts it, 'Scientific thought is not an accompaniment or condition of human progress, but human progress itself.'"

<sup>29</sup> The Grammar of Science, London, 1900.